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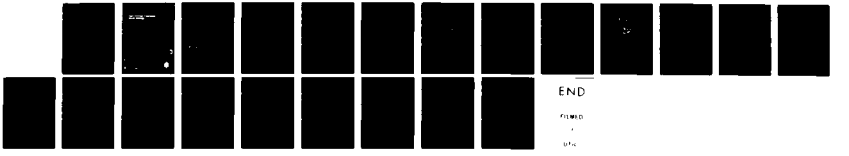

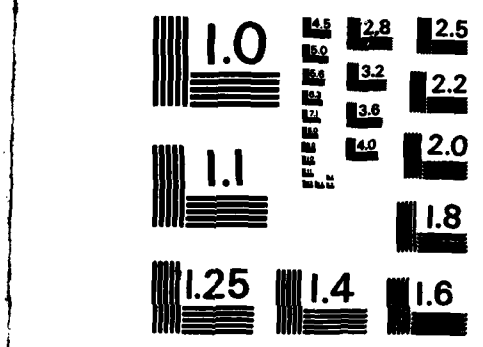

Report SAM-TR-82-28

MEDICAL APPLICATIONS OF BIOFEEDBACK – MOTION HYPERTENSION

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October 1982

Final Report for Period January 1982 – June 1982

USAF SCHOOL OF AEROSPACE MEDICINE
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NOTICES

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The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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This report provides an overview of the medical applications of radiofrequency-radiation (RFR) hyperthermia. RFR has limitations in focusing and penetration but can heat tissue selectively, on the basis of water content and dielectric properties. Nonionizing electromagnetic radiation may operate through several mechanisms, which are determined by the amount of energy deposited in tissues and the type of tissue irradiated. These attributes imply great versatility in the clinical applications of RFR. Furthermore, the synergistic activity of RFR with ionizing radiation and chemotherapy in cancer treatment increases

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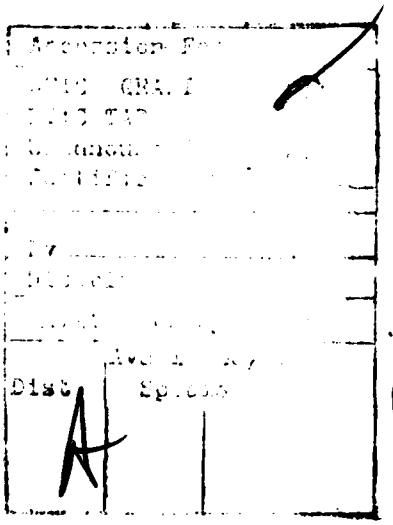
their effectiveness at lower doses. Lowered toxicity is a direct consequence of a lower effective dose in the presence of RFR. With improved therapeutic instrumentation and dosimetry and a better understanding of bioeffect mechanisms, the number of medical applications and the effectiveness of RFR should continue to increase.



MEDICAL APPLICATIONS OF RADIOFREQUENCY-RADIATION HYPERTHERMIA

INTRODUCTION

The application of heat for medical purposes dates back to antiquity. Instruments heated to high temperatures were used to cauterize wounds and burn away tumors. The use of hyperthermia to treat cancer has continued to be of interest. Busch (1) and others (2,3) observed that an endogenous source of hyperthermia, fever produced by bacterial infection, could cause tumor regression; and warm compresses, or local fomentations, were once used to treat tumors (4). Other hyperthermic techniques that have had some success in cancer treatment are water-bath immersion (5), ultrasound (6,7), hyperthermic regional perfusion (8), bacterial toxins (3,9), and total-body hyperthermia with heated anesthetic gases and hot wax (10,11).

Applying warmth to muscle, joint, and tendon injuries to relieve pain and accelerate healing is a common practice of both laymen and medical professionals. Diathermy, which grew out of this simple concept, is based on the heating of living tissue by resistance to electric currents flowing through the tissue. Radiofrequency-radiation (RFR) hyperthermia represents the most recent technology (7,12) in the art of hyperthermic healing.

Dosimetric studies of RFR (13-15), under the United States Air Force study of effects of radiofrequency electromagnetic radiation, have contributed greatly to understanding how RFR energy is coupled to the tissues of man and animals. The use of temperature changes in these studies to determine specific absorption rate (SAR) has yielded relations useful in predicting temperature rises in various tissues under various RFR conditions. Such data can be applied to therapeutic hyperthermic RFR dosimetry.

The purpose of this report is to introduce the reader to present and future medical applications of RFR hyperthermia. The references cite representative scientific literature on its various aspects.

BASIC PRINCIPLES AND INSTRUMENTATION

The production of heat by nonionizing electromagnetic radiation is based on the orientation of existing molecular (or atomic) dipoles in the electric field, the polarization of molecules (or atoms) in tissue to produce dipoles, and the displacement of "free" (conduction) electrons and ions in tissue (7,16,17). Resistance to the alignment and polarization of dipoles and to the flow of conducting electrons and ions in tissue results in heating (Fig. 1). Only the electric field within tissue produces heat, whether generated by an incident electric field or induced by an incident magnetic field. The transformation of electromagnetic energy into heat due to the friction of a material is called loss; and the material (e.g., tissue), a lossy material. The power absorbed is often expressed as the SAR in watts per

kilogram of tissue. The SAR is converted into temperature increase in tissue by the formula $1^{\circ}C/min = 58.6$ W/kg (15). This formula applies to tissue or tissue-equivalent material in which heat is not dissipated by blood circulation.

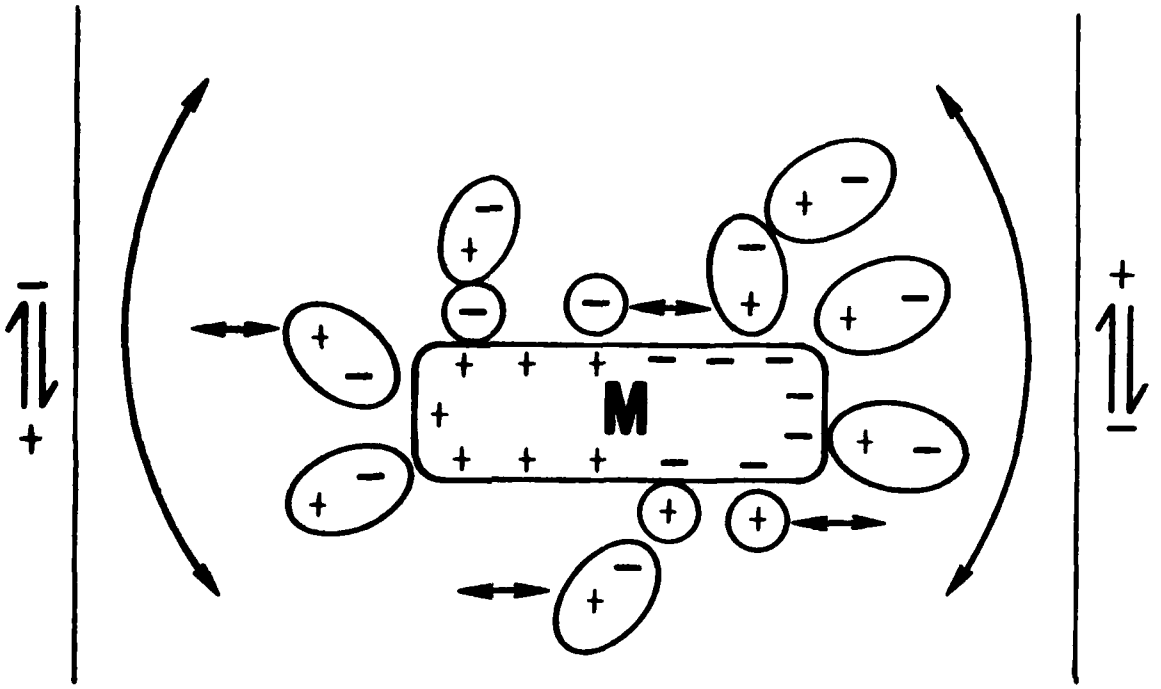


Figure 1. Rotation of a macromolecular dipole (M) induced by external alternating electromagnetic field. The friction of macromolecules with surrounding polar solvent molecules (water) and ions causes the solution to heat.

Using radiofrequency sources to heat tissue has certain limitations as well as advantages. A basic principle that should always be kept in mind when considering applications of microwave or high frequency hyperthermia is "the higher the frequency, the less penetrating the radiation." Another important principle is "the lower the frequency, the larger the area that must be exposed to RF radiation." This second principle is based on the relationship of wavelength to the dimensions of the object being irradiated and to the dimensions of the waveguide that is used to direct the radiation. In other words, longer wavelengths of RFR (lower frequencies) require longer dimensions for propagating and coupling objects.

These principles severely limit the energy-focusing ability of noninvasive radiative devices. The limitations must be reconciled with the fact that local hyperthermia is preferred over whole-body hyperthermia, because local high temperatures do not have the adverse effects of generalized high body temperature.

For a waveguide to propagate an electromagnetic wave efficiently, the longest dimension of the cross section of the guide must be equal to or greater than 0.5 the wavelength. Size restrictions of the waveguides (radiative aperture applicators) led to the common use of 2450-MHz RFR. However, at this frequency the power entering muscle tissue decayed to e^{-1} of its incident value at a depth of 0.85 cm (7). Waveguide applicators were then developed to function at 915 MHz (18-20), but the absorbed RFR power decayed to e^{-1} of its incident value at a depth of 1.5 cm in muscle tissue. The gain in depth was still too small.

The problem of waveguide dimensions has been partially overcome by filling waveguides with a low-loss dielectric (such as deionized water), providing them with internal longitudinal ridges, or filling them with dielectric strips (21,22). Such waveguides have smaller dimensions than conventional waveguides for high frequency RFR (3-30 MHz).

The selection of an appropriate frequency also depends on the size of the body or the part of the body to be irradiated. The absorption of RFR increases most rapidly when the largest dimension of the object being irradiated approaches 0.4 of a wavelength (13).

Localized hyperthermia has its own unique problems which may be turned into advantages. Under the same exposure conditions, objects of different dielectric properties and geometries heat differently. The greatest heating is likely to occur where such objects interface, especially if the E-field (electric-field component) is perpendicular to the interface (19). These facts provide a distinct advantage of RFR heating over hot-air heating or poorly penetrating infrared heating. Even though RFR may be difficult to focus, selecting an appropriate frequency and incident power density may permit selective heating of a tumor of a particular size and shape and with a higher water content than surrounding normal tissue (17). The tumor may be sealed off from surrounding tissue by interfacial heating.

With invasive techniques, such as the implantation of antennae (modified coaxial cables) or RF electrodes, the limited penetration and poor focusing of RFR need not be a disadvantage (23,24). A small uniform volume of tissue can be heated with a needle antenna, or larger but finely delineated volumes can be heated by an array of such antennae (25). Also, ferromagnetic "seeds" can be implanted in tissues and irradiated with an external magnetic field at frequencies below 2 MHz (26). Invasive techniques employ precise heating devices that do not have the limitations of noninvasive devices. Because implantation is required, however, invasive techniques have all the potential problems associated with surgery.

Current dosimetry is determined by invasive thermal probes such as thermistors, thermocouples, and temperature-sensitive crystals. With temperature changes, the crystals have altered light absorption, reflectivity, polarization, or fluorescence (27-33). Fiberoptics can therefore be used, without electrical conductors, to transmit temperature information to the recording equipment.

Noninvasive thermometric techniques now under study include measuring radiated microwave or millimeter-wave frequencies from tissue or measuring changes in velocity of sound in tissue as a function of tissue temperature (34-38).

Each type of temperature-measuring technique must meet certain criteria. All temperature probes must be sensitive, able to resolve temperature distribution, and able to respond rapidly to temperature change (39). Whatever device is used, it must not perturb the fields that heat the tissue, generate ohmic heating because of conducting materials (metals) within the device, or generate noise in the monitoring device due to the transfer of electric fields and currents induced by the incident RFR in wires.

The noninvasive devices for therapeutic delivery of RFR fall into three general categories: capacitive, inductive, and radiative aperture applicators (Fig. 2). I will discuss each briefly; further details can be found in the references (12,40-42).

The capacitive applicator is composed of two capacitor plates between which the tissue to be heated is placed. This method concentrates the heating at fat-muscle interfaces. The difference in dielectric properties of these two tissues generates the interface which the E-field vector transverses. This geometry leads to heating and damage to fat. However, this problem has been partially overcome by "cross firing" several capacitive plate pairs. The intersection of the heated volumes leads to an additive effect--heating the desired volume of tissue rather than heating fat at the interface (43).

Inductive applicators were developed to avoid the need for coupling medium or direct contact between the applicator and patient. The patient is placed in a large electromagnetic coil that induces currents within the body (44,45). The currents cause ohmic heating, but the heating patterns are complex and are not focused (7). Surface heating is likely to occur, and water or air cooling may be required.

Waveguide applicators were mentioned earlier as radiative aperture applicators. Several additional devices should be considered. One is a printed-circuit applicator from which power, at 2450 MHz, is radiated into tissues by many dipole antennae from a corporate feed. Another is a coaxial applicator composed of a semirigid 50-ohm coaxial cable with a Teflon-covered dipole antenna at the delivery end (22). The printed-circuit applicator is used to treat superficial tumors--breast cancer, in particular. The coaxial applicator is inserted rectally to treat prostate cancer.

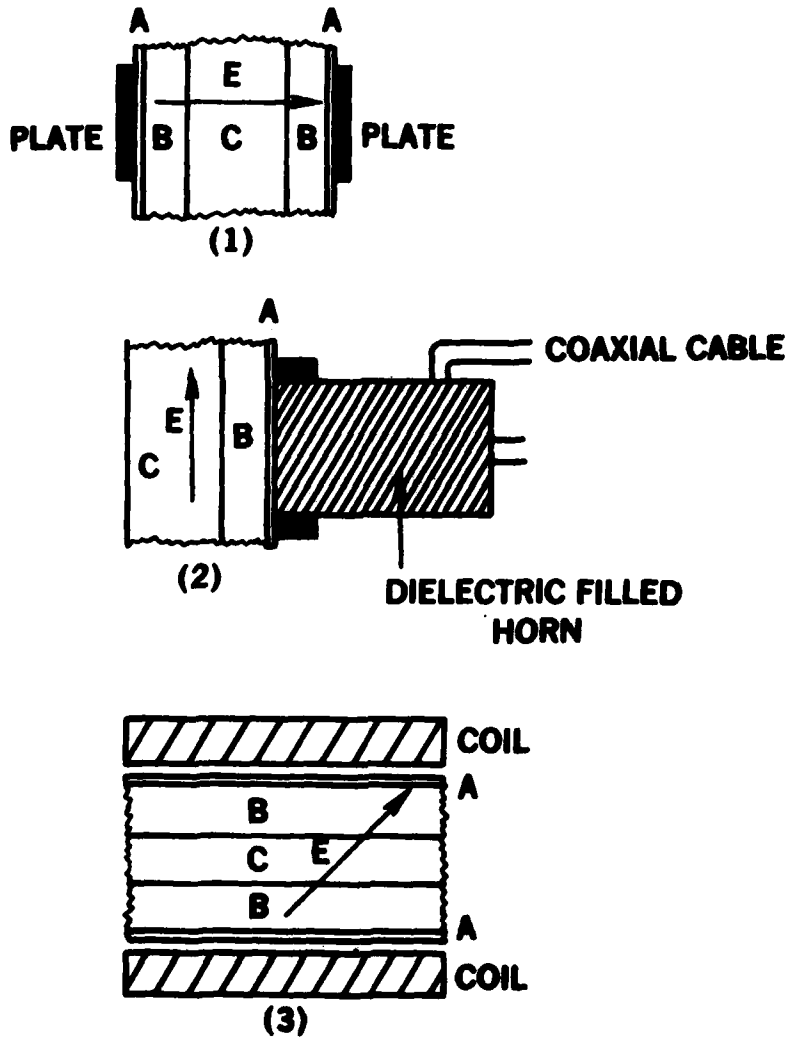


Figure 2. Noninvasive radiofrequency applicators for hyperthermia: (1) capacitive applicator; (2) dielectric-filled radiative aperture applicator; and (3) inductive applicator (magnetic coil). A, skin; B, fat; C, muscle and/or bone; and E, the electric-field vector (in a simplified fashion).

PRESENT APPLICATIONS

Clinical applications of RFR hyperthermia being actively pursued are (1) the local destruction of neoplasias; (2) stimulation of healing (especially bones); and (3) surgical removal of highly vascular or sequestered tissue. The first application is receiving the greatest attention at this time (46-48).

Although normal and neoplastic cells differ in sensitivity to hyperthermia (49-52), all tissues can be damaged by it. Lymphoid tissue is the most sensitive normal tissue. It is affected directly by hyperthermia (53,54) and indirectly by endogenous glucocorticosteroid release due to thermal stress (55,57).

The immunosuppressive effects, although transient, are an important disadvantage of whole-body or regional hyperthermia (53,54,58,59). In addition, insufficient hyperthermia--water-bath heating from 37°C to 42°C of Yoshida sarcomas in rats (60) and C3H mouse mammary carcinoma (61)--has led to increased metastasis and death. The response of tumors to hyperthermia during treatment must be closely monitored. However, local hyperthermia (42°C or greater), which has been effective against cancer, actually stimulates the immune response. Access of immunoresponsive and effector cells to solid tumors in man, by breakdown in the vasculature of the tumors after hyperthermia, probably plays a role in the complete destruction of tumors (44). In some cases, local RFR therapy has been followed by regression of metastasized tumors remote to the treatment site (22)--evidence for tumor destruction by immune stimulation.

In cancer therapy another advantage of RFR hyperthermia is that unlike ionizing radiation, it can attack cells during the synthetic (S) phase of the cell cycle (62,63). Furthermore, RFR hyperthermia and even euthermic RF exposure are synergistic with other cancer treatments. Human and animal tumors have demonstrated an increased sensitivity to ionizing radiation when RFR treatment is used simultaneously or within a short period of ionizing radiation treatments (49,64-71). A radioresistant fibrosarcoma in mice has shown dramatic responsiveness to ionizing radiation in combination with microwave hyperthermia, in spite of a lack of response to hyperthermia alone (64). Chemotherapy may also be enhanced by RFR therapy at incident power densities that are ineffective alone (69,72). Since the mechanisms that come into play in RFR destruction of neoplasias depend on the amount of energy absorbed, RFR can be used in a variety of cancer treatment regimens.

The potential of RFR as a healing stimulant has been demonstrated in experiments involving the healing of tooth-extraction wounds in dogs (73). These experiments should not be confused with the low frequency (75-Hz), pulsating, induced-direct-current studies being used clinically in man (with an approximate 75% success rate (74)) to stimulate healing of nonunion bone fractures, congenital pseudoarthroses, and failed fusions. Microwave radiation has also shown, in Chinese hamsters, significant promise as a radioprotective agent by stimulating rapid recovery from hematological damage caused by X-irradiation (75). Mild heat stress was probably responsible for the stimulation in both the tooth-extraction wounds and the damaged hematopoietic centers.

Another current application of RFR hyperthermia is the destruction of soft tissue by localized high-power-density microwave radiation. This surgical

technique is a sophisticated form of electrocautery. The induced currents destroy vasculature, thus minimizing bleeding and bringing about coagulation necrosis. The main difference in effect between RFR surgery and electrocautery is that the surgery can destroy larger volumes of tissue. Where very discrete small volumes of tissue are to be destroyed, as in hypophysectomy (76,77) or neurectomy (78,79), invasive needle antennae are used. They are precisely placed with the aid of radiography. Where larger volumes of tissue are to be removed, as in lung or hepatic lobectomies, external radiative aperture applicators can be used (80). In lung or liver resections with RFR surgery, the soft, friable tissue becomes condensed and solidified, thus making surgical removal nearly bloodless.

MECHANISMS

Mechanistic information related to clinical applications of RFR is primarily concerned with distinctions between the reactions of neoplastic and normal tissues. Neoplastic cells have been reported to differ from normal cells in RF absorption in the millimeter-wavelength range (81). Because of their limited penetration of tissue, however, these frequencies are not representative of RFR frequencies therapeutically applied, so such findings do not provide a valuable selectivity of RFR for tumor cells.

The activity of RFR hyperthermia against solid tumors appears to depend more on tumor physiology than on individual cell susceptibility. Tumors have a notoriously poor blood supply, which they tend to outgrow, often leading to central necrosis (82). When this already strained system is further stressed by hyperthermia from a RF source, heat cannot be dissipated as effectively as by surrounding normal tissue. Consequently, the temperature rises more rapidly in the tumor (83). At 42°C or more, vascular collapse, coagulation, hemorrhage, endothelial damage, thrombosis, and stasis may occur (82). As the temperature ascends, these changes become more severe. The higher water content of tumors as compared to normal tissue is also an important factor in their more rapid heating (17).

Lethal effects on the cellular level probably result from heat inactivation of enzymes, phase transitions in cell membranes which prevent essential functions, and acidification of the microenvironment of the cell (83-86). All cells should be sensitive to these changes, but to varying degrees. The DNA synthetic phase susceptibility could be explained by temperature-sensitive DNA repair enzymes or chromosomal proteins (84).

Slow or low-level heating of cells can generate thermotolerance (52,87). This tolerance could result from an increase in cholesterol or saturated fatty acids in the membranes of the cells. Such an increase would help maintain the form and integrity of the cell membranes by preventing a phase transition at higher temperatures. Slow or sublethal heating of the cells would allow time for such changes. No evidence, however, supports this hypothesis: no increase in cholesterol content has been observed in slowly heated cells (52). That increases in cholesterol content are responsible for thermotolerance is therefore doubtful.

Subpopulations of cells with thermostable key enzymes could also be selected by slow heating or elevated but sublethal temperatures, but this population change should be even slower than a membrane adaptation and therefore would be less likely to occur. Furthermore, the rapid loss of thermotolerance (within 20 to 72 hours) that has been observed after return to normal temperatures tends to discredit this latter hypothesis (87-89). The only change that correlates with thermotolerance is an increase in membrane protein (52).

When only enough RFR energy is absorbed to raise the temperature of tumors from 37°C to 41°C, previously mentioned killing mechanisms (e.g., protein denaturation, acidification of tumor, membrane changes, and hemodynamic changes) are not operable. At these levels, vascular collapse does not occur and vascular effects are reversible (82). At 41°C and below, blood flow to tumors actually increases and oxygen tension rises (83); but at these levels apparent oxygen-independent sensitivity (as opposed to a real oxygen independence) of cells to ionizing radiation is enhanced (90). Clostridium oncolyticum s. butyricum spores will germinate in tumors treated with RFR and ionizing radiation (91). (In the experiments, these tumors reached local temperatures of between 40°C and 41°C.) The growth of a fastidiously anaerobic bacterium in such tumors demonstrates an unexplained complete depletion of oxygen in the tumors (91). Based on the hemodynamic response at 40°C to 41°C, these tumors should have had an increase in their oxygen tensions with RFR hyperthermia alone. Free-radical reactions that consume oxygen and are initiated by ionizing radiation or mitochondrial oxidative metabolism may be enhanced by the energy input from RFR hyperthermia.

Organic free radicals may interact with available oxygen and rapidly deplete it. After this removal of oxygen, other toxic free-radical reactions independent of oxygen could be maintained by thermal energy from the RFR. The series of reactions shown in Figure 3 describes a possible free-radical mechanism that could occur in cell membrane lipids. The thermal decomposition of organic peroxides formed by ionizing radiation and oxygen (even low levels) or of naturally occurring organic peroxides could provide the initiator for such a polymerization scheme.

As alluded to earlier, an immunological mechanism probably plays some role in tumor rejection after RFR therapy. Exposure of tumors to 41°C or less may have a secondary immunostimulatory effect on lymphocytes circulating through the tumor vasculature or in nearby lymphoid tissues (44). Exposure of human lymphocytes in vitro to temperatures of 38°C to 40°C, inclusive, enhances the lymphoblastic response to mitogens (92-94). Such evidence supports the possibility of immunostimulation by in vivo hyperthermia in man. This stimulation could aid the immune system in overcoming tumor-induced immunosuppression.

FUTURE APPLICATIONS

The probable mechanisms of RFR interaction with biological systems suggest additional medical applications. One application, yet to be pursued in a practical way, is immune modulation with RFR hyperthermia. Increasing the temperature of the body or lymphoid organs to 41°C should provide immunostimulatory activity. This effect could be used to reverse the immunosuppression of chemotherapy, ionizing radiation, and various infectious diseases. Exposures

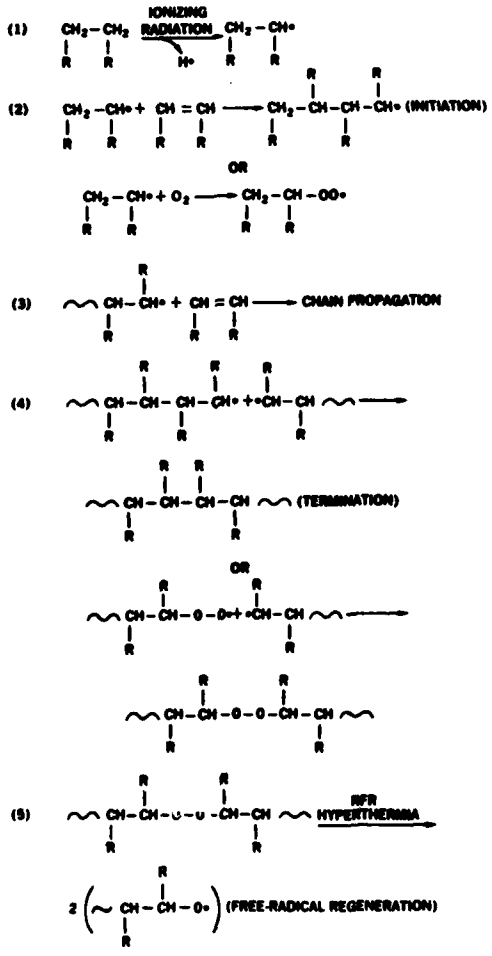


Figure 3. Theoretical free-radical chain reaction of unsaturated lipids that may be stimulated by RFR hyperthermia.

raising body temperature or lymphoid organ temperature to 42°C or above for short periods of time could be used to bring about immunosuppression for control of autoimmune disease and cell-mediated hypersensitivity.

Another possibility is the use of RFR hyperthermia in treating shock. To relieve metabolic demands for heat production, and therefore lower the requirement for oxidative metabolism, heat could be supplied externally by whole-body or regional hyperthermia. The neurological and endocrine systems would be recruited through their thermoregulatory functions to decrease the demand for metabolic heat production. As a result, cardiac output, although compromised, would again become sufficient to maintain life. Such support would provide crucial time required to reestablish normal cardiac output.

The oxidative metabolism of specific organs, such as the liver, may be stimulated within a certain temperature range to increase detoxification. This function may aid in the recovery from toxic shock. The synergistic activity of RFR with ionizing radiation suggests that free-radical reactions may thus be modulated. Oxidases and peroxidases, which are widespread in tissue and of great importance to the immune system, are radiomimetic enzymes. In fact they generate the same oxygen and organic radicals found during the radiolysis of biological materials. These enzymes are cytotoxic for neoplastic cells (95). Since oxidative enzymes comprise in vivo "free" electron systems, the antitumor activity of exogenously introduced oxidases and peroxidases should be enhanced by RFR hyperthermia, as is the activity of ionizing radiation. The principal advantage of combined RFR oxidative enzyme therapy would be its anticipated low toxicity for normal tissue.

REFERENCES

1. Busch, W. Ulber den einfluss welchen heftigere erysipeln zuweilen auf organisierte neubildungen ausiiben. Verhandl, Naturh-Preuss, Rhein Westpahl 23:28-30 (1866).

2. Bruns, P. Die heilwirkung des erysipels auf geschwulste. Beitr Klin Chir 3:443 (1887).

3. Coley, W. B. Late results of the treatment of inoperable sarcoma by the mixed toxins of erysipelas and bacillus prodigiosus. Am J Sci 131:375 (1906).

4. Percy, J. F. Heat in the treatment of carcinomas of the uterus. Surg Gynecol Obstet 22:77 (1915).

5. Crile, G., Jr. The effects of heat and radiation on cancers implanted on the feet of mice. Cancer Res 23:372-380 (1963).

6. Selawry, O. S., J. C. Carlson, and G. E. Moore. Tumor response to ionizing rays at elevated temperatures: A review and discussion. Am J Roentgenol 80:833-839 (1958).

7. Christensen, D. A., and C. H. Durney. Hyperthermia production for cancer therapy: A review of fundamentals and methods. J Microwave Power 16:89-105 (1981).

8. Cavaliere, R., E. C. Ciocatto, B. C. Giovanella, et al. Selective heat sensitivity of cancer cells: Biochemical and clinical studies. Cancer 20(3):1351-1381 (1967).

9. Coley, W. B. The treatment of malignant tumors by repeated inoculations of erysipelas with a report of original cases. Am J Med Sci 105:487-511 (1893).

10. Henderson, M. A., and R. T. Pettigrew. Induction of controlled hyperthermia in treatment of cancer. Lancet 1:1275-1277 (1971).

11. Pettigrew, R. T., J. M. Galt, C. M. Ludgate, and A. N. Smith. Clinical effects of whole-body hyperthermia in advanced malignancy. Br Med J 4:679-682 (1974).

12. Kantor, G. Evaluation and survey of microwave and radiofrequency applicator. J Microwave Power 16:135-150 (1981).

13. Johnson, C. C., C. H. Durney, P. W. Barber, et al. Radiofrequency radiation dosimetry handbook, 1st ed. SAM-TR-76-35, Sep 1976.

14. Durney, C. H., C. C. Johnson, P. Barber, et al. Radiofrequency radiation dosimetry handbook, 2d ed. SAM-TR-78-22, May 1978.

15. Durney, C. H., M. F. Iskander, H. Massoudi, et al. Radiofrequency radiation dosimetry handbook, 3d ed. SAM-TR-80-32, Aug 1980.

16. Grant, E. H., R. J. Shepard, and G. P. South. Dielectric behavior of biological molecules in solution. Oxford: Clarendon Press, 1978.

17. Foster, K. R., and J. L. Schepps. Dielectric properties of tumor and normal tissues at radio through microwave frequencies. J Microwave Power 16:107-119 (1981).

18. Guy, A. W. Electromagnetic fields and relative heating patterns due to rectangular aperture source in direct contact with bi-layered biological tissue. IEEE Trans Microwave Theory Tech MTT-19:214-223 (1971).

19. Guy, A. W., J. F. Lehmann, and J. B. Stonebridge. Therapeutic applications of electromagnetic power. Proc IEEE 62:55-75 (1974).

20. Guy, A. W., J. F. Lehmann, J. B. Stonebridge, and C. C. Sorensen. Development of a 915-MHz direct-contact applicator for therapeutic heating of tissue. IEEE Trans Microwave Theory Tech MTT-26:550-556 (1978).

21. Cheung, A. Y., T. Dao, and J. E. Robinson. Dual-beam TEM applicator for direct-contact heating of dielectrically encapsulated malignant mouse tumor. Radio Sci 12(6S):81-85 (1977).

22. Sterzer, F., R. W. Paglione, J. Mendecki, et al. RF therapy for malignancy: Heating of malignant tissues (hyperthermia) by RF radiation presents a new tool in the arsenal of weapons against cancer. IEEE Spectrum 17:32-37 (1980).

23. Taylor, L. S. Implantable radiators for cancer therapy by microwave hyperthermia. Proc IEEE 68:142-149 (1980).

24. Doss, J. D., and C. W. McCabe. A technique for localized heating in tissue: an adjunct to tumor therapy. Med Instrum 10:16-21 (1976).

25. Trembly, B. S., J. W. Strohbehn, D. C. deSieyes, and E. B. Douple. Hyperthermia induced by an array of invasive microwave antennas. (Paper Te-41) In The third international symposium: Cancer therapy by hyperthermia, drugs, and radiation. Fort Collins: Colorado State University, June 22-26, 1980.

26. Stauffer, P. R., T. C. Cetas, and R. C. Jones. A system for producing localized hyperthermia in tumors through magnetic induction heating of ferromagnetic implants. (Paper Te-35) In The third international symposium: Cancer therapy by hyperthermia, drugs, and radiation. Fort Collins: Colorado State University, June 22-26, 1980.

27. Rozzell, T. C., C. C. Johnson, C. H. Durney, et al. A nonperturbing temperature sensor for measurements in electromagnetic fields. J Microwave Power 9:241-249 (1974).

28. Plumb, H. H. (ed.). Temperature, its measurement and control in science and industry. Pittsburg: Instrument Society of America, 1972.

29. Johnson, C. C., O. P. Gandhi, and T. C. Rozzell. A prototype liquid crystal fiberoptic probe for temperature and power measurements in RF field. Microwave J 18:55-59 (1975).

30. Quin, T. J., and J. P. Compton. The foundations of thermometry. Prog Phys 38:151-239 (1975).

31. Cetas, T. C., and W. G. Conner. Thermometry considerations in localized hyperthermia. Med Phys 5:79-91 (1978).

32. Cetas, T. C. Division of Electronic Products, Bureau of Radiological Health. A birefringent crystal optical thermometer for measurements in electromagnetically induced heating. In C. C. Johnson and M. L. Shore (eds.). Biological effects of electromagnetic waves (Vol II), pp. 338-348. Rockville, US Dep Health, Education, and Welfare, HEW Publication (FDA) 77-8011, 1976.

33. Christensen, D. A. Thermal dosimetry and temperature measurements. Cancer Res 39:2325-2327 (1979).

34. N'Guyen, O. D., A. Mamouni, Y. Leroy, and E. Constant. Simultaneous microwave local heating and microwave thermography: Possible clinical applications. J Microwave Power 14:135-137 (1979).

35. Robert, J., J. Edrich, P. Thouvenot, M. Gautherie, and J. M. Escayne. Millimeter-wave thermography: Preliminary clinical findings in heat and neck diseases. J Microwave Power 14:131-134 (1979).

36. Gautherie, M., J. Edrich, R. Zimmer, J. L. Guerguin-Kern, and J. Robert. Millimeter-wave thermography--Application to breast cancer. J Microwave Power 14:123-129 (1979).

37. Johnson, S. A., D. A. Christensen, C. C. Johnson, J. F. Greenleaf, and B. Rajagopalan. Nonintrusive measurement of microwave and ultrasound-induced hyperthermia by acoustic temperature tomography. Ultrasonic Symp Proc IEEE 1264-ISV:977-982 (1977).

38. Nasoni, R. L., T. Bowen, W. G. Connor, and R. R. Sholes. Temperature dependence of ultrasonic speed in tissue and its application to non-invasive temperature monitoring. Ultrasonic Imaging 1:34-43 (1979).

39. Bowman, H. F. Heat transfer and thermal dosimetry. J Microwave Power 16:121-133 (1981).

40. Cheung, A. Y., W. M. Golding, and G. M. Samaras. Direct contact applicators for microwave hyperthermia. J Microwave Power 16:151-159 (1981).

41. Samaras, G. M., H. W. VanHorn, V. F. King, E. L. Slawson, and A. Y. Cheung. Clinical hyperthermia systems engineering. J Microwave Power 16:161-169 (1981).

42. Gibbs, F. A., Jr. Clinical evaluation of a microwave/radiofrequency system (BSD Corporation) for induction of local and regional hyperthermia. J Microwave Power 16:185-192 (1981).

43. Sugaar, S., and H. H. LeVeen. A histopathologic study on the effects of radiofrequency thermotherapy on malignant tumors of the lung. Cancer 43:767-783 (1979).

44. Storm, F. K., W. H. Harrison, R. S. Elliot, and D. L. Morton. Normal tissue and solid tumor effects of hyperthermia in animal models and clinical trials. Cancer Res 39:2245-2251 (1979).

45. Storm, F. K., W. H. Harrison, R. S. Elliot, L. R. Kaiser, A. W. Silberman, and D. L. Morton. Clinical radiofrequency hyperthermia by magnetic-loop induction. J Microwave Power 16:179-184 (1981).

46. Michaelson, S. M., and H. P. Schwan. Factors governing the use of microwave/radiofrequency energies in cancer therapy. Adv in Rad Biol 9:323-409 (1981).

47. Gilbert, E. H., D. A. Pistenma, and F. K. Mahoney. Hyperthermia--Research supported by the National Cancer Institute. J Microwave Power 16:227-231 (1981).

48. Miller, R. C., W. G. Conner, R. S. Heusinkveid, and M. L. M. Boone. Prospects for hyperthermia in human cancer therapy. Part I: Hyperthermic effects in man and spontaneous animal tumors. Radiology 123:489-495 (1977).

49. Connor, W. G., E. W. Gerner, R. C. Miller, and M. L. M. Boone. Prospects for hyperthermia in human cancer therapy. Part II: Implications of biological and physical data for applications of hyperthermia to man. Radiology 123:497-503 (1977).

50. Magin, R. L., and R. K. Johnson. Effects of local tumor hyperthermia on the growth of solid mouse tumors. Cancer Res 34:4534-4539 (1979).

51. Marmor, J. B., N. Hahn, and G. M. Hahn. Tumor cure and cell survival after localized radiofrequency heating. Cancer Res 37:879-883 (1977).

52. Herman, T. S., E. W. Gerner, B. E. Magun, et al. Rate of heating as a determinant of hyperthermic cytotoxicity. Cancer Res 41:3519-3523 (1981).

53. Shah, S. A., and J. A. Dickson. Effect of hyperthermia on the immunocompetence of VX2 tumor-bearing rabbits. Cancer Res 38:3523-3531 (1978).

54. Shah, S. A., and J. A. Dickson. Effect of hyperthermia on the immune response of normal rabbits. Cancer Res 38:3518-3522 (1978).

55. Huang, A. T., M. E. Engel, J. A. Elder, et al. The effect of microwave radiation (2450 MHz) on the morphology and chromosomes of lymphocytes. Radio Sci (Suppl) 12:173-177 (1977).

56. Prince, J. E., L. H. Mori, J. W. Frazer, and J. C. Mitchell. Cytologic aspect of radiofrequency radiation in the monkey. Aerospace Med 43:759-761 (1972).

57. Liburdy, R. P. Radiofrequency radiation alters the immune system: Modulation of T- and B-lymphocyte levels and cell-mediated immunocompetence. Radiat Res 77:34-46 (1979).

58. Szmigielski, S., W. Roszkowski, M. Kobus, and J. Jelijaszewicz. Modification of experimental acute staphylococcal infections by long-term exposition to non-thermal microwave fields or whole-body microwave hyperthermia. In A. J. Berteaud and B. Servantie (eds.). Ondes Electromagnetiques et Biologie. Proc 1980 URSI/CNFRS Int Symp Electromagnetic Waves and Biology, p. 127. Jouy-en-Josas, France: International Union of Radio Science, June 30-July 4, 1980.

59. Szmigielski, S., A. Szudzinski, A. Pietraszek, and M. Bielec. Acceleration of cancer development in mice by long-term exposition to 2450 MHz microwave fields. In A. J. Berteaud and B. Servantie (eds.). Ondes Electromagnetiques et Biologie. Proc 1980 URSI/CNFRS Int Symp Electromagnetic Waves and Biology, p. 165. Jouy-en-Josas, France: International Union of Radio Science, June 30-July 4, 1980.

60. Dickson J. A., and H. A. Ellis. The influence of tumor volume and the degree of heating on the response of the solid Yoshida sarcoma to hyperthermia (40-42°C). Cancer Res. 36:1188-1195 (1976).

61. Walker, A., H. M. McCallum, T. E. Wheldon, et al. Promotion of metastasis of C3H mouse mammary carcinoma by local hyperthermia. Br J Cancer 38:561-563 (1978).

62. Dewey, W. C., and R. M. Humphrey. Survival of mammalian cells irradiated in different phases of the life-cycle as examined by autoradiography. Nature 198:1063-1066 (1963).

63. Westra, A., and W. C. Dewey. Variation in sensitivity to heat shock during the cell cycle of Chinese hamster cell in vitro. Int J Radiat Biol 19:467-477 (1971).

64. Yerushalmi, A. Cure of a solid tumor by simultaneous administration of microwaves and X-ray irradiation. Radiat Res 64:602-610 (1975).

65. Suit, H. D. Hyperthermic effects on animal tissues. Radiology 123: 483-487 (1977).

66. Corry, P. M. S., S. Robinson, and S. Getz. Hyperthermia effects on DNA repair mechanisms. Radiology 123:475-482 (1977).

67. Hymmen, U., and C. Weiland. Combined treatment of radioresistant malignant tumors with high frequency hyperthermia and gamma-rays therapy--Recent results. J Microwave Power 14:173-180 (1979).

68. Nelson, A. J. M., and J. A. G. Holt. Combined microwave therapy. Med J Aust 2:88-90 (1978).

79. Nelson, A. J. M., and J. A. C. Holt. Microwave adjuvant to radiotherapy and chemotherapy for advanced lymphoma. Med J Aust 1:311-313 (1980).

70. Hornback, N. B., R. Shupe, H. Shidnia, et al. Radiation and microwave therapy in the treatment of advanced cancer. Radiology 130:459-464 (1979).

71. Raymond, U., K. T. Noell, K. T. Woodward, B. T. Worde, R. I. Fishburn, and L. S. Miller. Microwave-induced local hyperthermia in combination with radiotherapy of human malignant tumors. Cancer 45(1):638-646 (1980).

72. Chang, B. K., A. T. Huang, and W. T. Joines. Inhibitation of DNA synthesis and enhancement of the uptake and action of methotrexate by low-power-density microwave radiation in L1210 leukemia cells. Cancer Res 40: 1002-1005 (1980).

73. Cook, H. H., N. N. Soni, and J. C. Montgomery. The effects of pulsed, high frequency radiowaves on the rate of osteogenesis in the healing of extraction wounds in dogs. Oral Surg 32:1008-1016 (1971).

74. Bassett, C. A., S. Mitchell, L. Norton, et al. Electromagnetic repair of nonunions. In C. T. Brighton, J. Black, and S. R. Pollack (eds.). Electrical properties of bone and cartilage, p. 605. New York: Grune and Stratton, 1979.

75. Lappenbusch, W. L., L. J. Gillespie, W. M. Leach, and G. E. Anderson. Effect of 2450-MHz microwaves on the radiation response of X-irradiated Chinese hamsters. Radiat Res 54:294-303 (1973).

76. Zervas, N. T. Stereotaxic radiofrequency surgery of the normal and the abnormal pituitary gland. N Engl J Med 280:429-437 (1969).

77. Zervas, N. T., and H. Hamlin. Stereotactic radiofrequency hypophysectomy. Appl Neurophysiol 41:219-222 (1978).

78. Rosomoff, H. L. Bilateral percutaneous cervical radiofrequency cordotomy. J Neurosurg 31:41-46 (1969).

79. Onofrio, B. M. Radiofrequency percutaneous Gasserian ganglion lesions. Results in 140 patients with trigeminal pain. J Neurosurg 42(1):132-139 (1975).

80. Osaka, A. Use of microwave radiation in surgery and cancer therapy. J Microwave Power 13:155-161 (1978).

81. Webb, S. J., and A. D. Booth. Microwave absorption by normal and tumor cells. Science 174:72-74 (1971).

82. Eddy, H. A. Alterations in tumor microvasculature during hyperthermia. Radiology 137:515-521 (1980).

83. Bicher, H. I., F. W. Hetzel, T. S. Sandhu, et al. Effects of hyperthermia on normal and tumor microenvironment. Radiology 137:523-530 (1980).

84. Dewey, W. C., L. E. Hopwood, S. A. Sapareto, and L. E. Gerweck. Cellular responses to combinations of hyperthermia and radiation. Radiology 123:463-474 (1977).

85. Overgaard, J., and P. Bichel. The influence of hypoxia and acidity on the hyperthermic response of malignant cells in vitro. Radiology 123:511-514 (1977).

86. Zanker, K. S., R. Jung, D. Stavrou, and G. Blumel. Influence of microwave irradiation on cultured glioma cells. I. An enzymatic and scanning electron microscopy study. J Microwave Power 14:159-162 (1979).

87. Harisiadis, L., D. Sung, and E. J. Hall. Thermal tolerance and repair of thermal damage by cultured cells. Radiology 123:505-509 (1977).

88. Gerner, E. W., and M. J. Schneider. Induced thermal resistance in HeLa cells. Nature 256:500-502 (1975).

89. Gerner, E. W., R. Boone, W. G. Connor, et al. A transient thermotolerant survival response produced by single thermal doses in HeLa cells. Cancer Res 36:1035-1040 (1976).

90. Robinson, J. E., M. J. Wizenberg, and W. A. McCready. Combined hyperthermia and radiation suggest an alternative to heavy particle therapy for reduced oxygen enhancement ratios. Nature 251:521-522 (1974).

91. Gericke, D., F. Dietzei, and I. Ruster. Further progress with oncolysis due to local high frequency hyperthermia, local X-irradiation, and apathogenic clostridia. J Microwave Power 14:163-166 (1979).

92. Roberts, N. J., and R. T. Steigbigel. Hyperthermia and human leukocyte functions: Effects on response of lymphocytes to mitogen and antigen and bactericidal capacity of monocytes and neutrophils. Infect Immun 18:673-679 (1977).

93. Ashman, R. B., and A. J. Nahmias. Effect of incubation temperature on mitogen responses of lymphocytes from adult peripheral blood and from cord blood. Clin Exp Immunol 33:319-326 (1978).

94. Smith, J. B., R. P. Knowlton, and S. S. Agarwal. Human lymphocyte responses are enhanced by culture at 40°C. J Immunol 121:691-694 (1978).

95. Kiel, J. L. The cytotoxic activity of peroxidases (PhD dissertation, Texas Tech Health Sciences Center, Lubbock, Tex.). Ann Arbor, Mich.: Xerox University Microfilms International, 1981.